REMARKS

I. Status of the Claims

Claims 1-5, 12-14, 16-66, 73, 74, 76-85, 87-92 and 100 are pending. Claims 4, 5, 62-66, 79-85, 87-93 and 100 have been withdrawn from consideration. Claims 1-3, 12-14, 16-61, 73, 74 and 78 have been examined.

II. Response to the Office Action

A. Finality of the Office Action

Applicants note that the finality of the Office Action has been withdrawn by virtue of the Petition Decision dated March 4, 2010.

B. Restriction Requirement

The Petition Decision dated December 4, 2009 noted that the restriction requirement was made without properly following the procedure set forth in MPEP 1893.03(d) and directed the Examiner, upon resuming examination, "to reevaluate the claims as amended to determine whether they have unity of invention." Petition Decision dated December 4, 2009, p. 9. The Director also directed the Examiner to "consider whether or not the method claims currently pending have unity of invention with the claimed compounds." *Id.*

The Office Action dated December 17, 2009 states that "Examiner still considers the claims as presented in the amendment filed on June 9, 2009 to lack unity of invention", Office Action p. 2, yet the Office fails to provide any reasoning whatsoever to support this conclusion. The Office Action also makes no mention of unity of invention among the compound and method claims despite the Director's explicit instruction to reconsider this issue.

The reference cited in the rejection under 35 U.S.C. § 102(e) fails to establish that the claims lack unity of invention for at least two reasons. First, the reference fails to "break the unity" of the claims for at least for the reasons explained below addressing the rejection under 35 U.S.C. § 102(e), showing that the Office is incorrect in its assessment that the reference anticipates the claims. Since the Office's assertion that the claims lack novelty over the Griffith

reference is incorrect, there is no evidence of record demonstrating that the combination of structural features defined by the compound definition in claim 1 fails to represent a contribution to the art. Second, the reference is not properly considered as prior art for the purpose of evaluating unity of invention because it was published after the international filing date of the present application. Unity of invention is determined under the P.C.T. Rules. *See Caterpillar Tractor Co.*, 650 F.Supp. at 220. P.C.T. Rule 33.1 defines the relevant prior art for the International Search as "everything which has been made available to the public anywhere in the world by means of written disclosure ... *provided that the making available to the public occurred prior to the international filing date*" thereby excluding references published after the international filing date.[1] P.C.T. Rule 33.1 (emphasis added). Patent applications which are unpublished as of the international filing date therefore are clearly not considered "prior art" under the P.C.T. rules and do not qualify as prior art for the purpose of determining unity of invention.

Based on the foregoing, Applicants respectfully submit that there is no basis for the Office's position that the claims as presently pending lack unity of invention.

C. Withdrawn Objections

Applicants thank the Examiner for withdrawing the objection to the Abstract and the objection to the Drawings. Applicants also thank the Examiner for withdrawing the objection to claims as containing non-elected subject matter.

D. Claim Rejections

1. Rejection of Claims 1-3, 12-14, 16-61, 73, 74 and 78 under the Enablement Requirement of 35 U.S.C. § 112, First Paragraph

Claims 1-3, 12-14, 16-61, 73, 74 and 78 were rejected under the Enablement Requirement of 35 U.S.C. § 112, first paragraph. The Office Action acknowledges that the claims are enabled for a pyrimidinyl when N-A-B-D is a piperidinyl or piperazinyl ring, Ar_1 is a

[1] Rule 33.1(c) specifically indicates that an application filed or having an earlier priority date but published later than the application being examined is not such "relevant prior art" (but rather is art that *would* constitute relevant prior art "*had it been published prior* to the international filing date." (emphasis added))

phenyl or fused phenyl ring, but alleges that the specification does not reasonably provide enablement for "any other groups, or any hydrates or solvates within the scope of claim 1."

The Office is respectfully reminded that Applicants enjoy a presumption that the specification, which discloses how to make and use the claimed invention, complies with the first paragraph of 35 U.S.C. § 112. MPEP 2164.04 (citing *In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971)). Under the presumption, the enablement requirement must be considered to be satisfied unless and until there is a reason to doubt the objective truth of the specification, and the initial burden of establishing a basis for denying patentability to a claimed invention therefore rests upon the examiner. *Id. See also In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988); *In re Thorpe*, 777 F.2d 695 (Fed. Cir. 1985); *In re Piasecki*, 745 F.2d 1468 (Fed. Cir. 1984). "It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which *is inconsistent* with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." MPEP 2164.04 (citing *In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971)).

An application satisfies the enablement requirement if the disclosure has sufficient information to enable the person skilled in the pertinent art to make and use the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The test for whether experimentation would be undue is not merely quantitative since a considerable amount of experimentation is permissible, if it is merely routine. *Id* at 737. The fact that experimentation may be required and may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. on other grounds sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985). *See also In re Wands*, 858 F.2d at 737. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976).

The question as to whether the application enables the person of ordinary skill in the art to make the compounds of the invention is whether he can do so without undue experimentation, using the disclosure of the application, the knowledge of one of ordinary skill in the art, and applying an ordinary level of creativity to the problem. It is not necessary for "a patent specification to become a catalogue of existing technology", and "[a] patent specification need not teach, and preferably omits, what is well known in the art." MPEP 2182 (citing *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986)). Furthermore, "[a] person of ordinary skill is also a person of ordinary creativity, not an automaton." *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1742 (2007). The Office fails to provide reasoning or analysis sufficient to raise a *bona fide* issue that the claims of the present application lack enablement.

a. The Office has failed to provide a Complete Response to Applicants' Traversal of the Rejection as Filed on June 9, 2009

MPEP 707.07(e) instructs Examiners that:

> In order to provide a complete application file history and to enhance the clarity of the prosecution history record, an examiner must provide clear explanations of all actions taken by the examiner during prosecution of an application.
>
> Where the requirements are traversed, or suspension thereof requested, the examiner should make proper reference thereto in his or her action on the amendment.
>
> *Where the applicant traverses any rejection, the examiner should, if he or she repeats the rejection, take note of the applicant's argument and answer the substance of it.*

MPEP 707.07(e) (emphasis added).

In response to the rejection made in the Office Action dated March 9, 2009, Applicants provided a thorough and detailed response comprehensively addressing the substance of the Office's rejection made under 35 U.S.C. § 112, first paragraph. *See* Response to Office Action filed June 9, 2009, at pp. 44-61. In response to Applicants' seventeen *page* traversal in their response filed on June 9, 2009, the Office provides an eighteen *line* response in the Office Action dated December 17, 2009, which entirely fails to answer the substance of many of the points of Applicants' argument. The Office states:

> Applicants have argued first that the examiner misidentified the structures as "triazolopyrimidines and pyrazolopyrimidines" instead of just pyrimidines. Applicants are correct and this typographical error has been corrected.
>
> Second, Applicants have argued that solvates and hydrates have been reasonably enabled, examiner disagrees. Vippagunta, et. al. does explain that solvates and hydrates do exist, yes, and goes on to state that as many as 1/3 of all pharmaceuticals MAY form hydrates or solvates. However, the Applicants have not shown in any reasonable way that they have enabled compounds to form solvates or hydrates, they merely believe that some of them will form arguing probability. Applicants have not pinpointed which compounds will form a solvate, which will form a hydrate, which may form both and which will form neither. They merely speculate that because there is a chance of formation, that this must be good enough. Applicants must teach the current invention limitation of solvates and hydrates, which they do not. Vippagunta states that the formation of solvates and hydrates is unpredictable, therefore merely stating that exposing a compound to water or a solvent will generate the hydrate or solvate is completely false, as stated prior, 2/3 of all pharmaceuticals will NOT form the hydrate or solvate. No new matter permitted. Appropriate correction is required.

Office Action dated December 17, 2009 pp. 3-4.

Applicants response argued, among other things: (1) that the reasons for the rejection did not appear to relate to the disclosure of the present application; (2) that the Office improperly disregarded the presumption of enablement to which Applicants are entitled, that the Office had failed to cite any evidence inconsistent with enablement of Applicants' claims sufficient to overcome the presumption of enablement, and that the Office instead improperly imposed a requirement on Applicants to probe enablement of their claims; (3) that there was no requirement to provide working examples of every substituent option to provide adequate support for a Markush claim; (4) that over 300 examples had, in fact, been provided, with examples going beyond the scope for which enablement was acknowledged (even though there was no requirment to provide examples of every substitutent option); (5) that the Dörwald reference cited by the Office contradicted the Office's assertion that "chemistry is unpredictable" because it recites that most chemistry textbooks and research articles describe that organic chemical reactions proceed smoothly, that the reference was irrelevant insofar as it describes unpredictability in the synthesis of complex natural products; (6) that Vippagunta describes that solvates and hydrates are ubiquitous; (7) that the literature showed that hydrates and solvates

could be made by routine experimentation (an assertion Applicants supported with *evidence* in the form of the Guillory, Vippagunta and Morisette references); (8) that the Office's reasoning in support of the enablement rejection unduly emphasized the alleged unpredictability of chemistry in general and forming solvates in particular, while disregarding evidence of routine methods available in the art for synthesis and screening (including synthesis and screening of solvates) – the same error that was reversed by the Federal Circuit in *Wands*; and (9) that the Office Action in making the rejection failed to consider all the *Wands* factors together. Applicants also provided a detailed discussion of each of the *Wands* factors, pointing out how consideration of all the relevant factors should lead to a conclusion that the claims were adequately enabled.

Applicants respectfully submit that the Office's response to Applicants' arguments provided in the Office Action dated December 17, 2009 failed to answer the substance of Applicants' argument, since most of the points made by the Applicants were completely ignored by the Office in maintaining the rejection.

b. It Remains Unclear from the Record Whether the Office Has Given Any Significant Consideration to the Disclosure of the Present Application in Making the Rejection Under the Enablement Requirement of 35 U.S.C. 112, First Paragraph.

In their response mailed on June 9, 2009, Applicants remarked that the reasons given in the Office Action dated March 9, 2009 did not appear to relate to the disclosure of the present application. Applicants noted a statement in the Office Action dated March 9, 2009 alleging that the present application described "how to make triazolopyrimidines and pyrazolopyrimidines" whereas, in fact, the present application does not specifically discuss any triazolopyrimidines or triazolopyrimidines. Applicants suggested that the Office's remarks in making the enablement rejection appeared to refer to a different application, having a different specification (one apparently that described triazolopyrimidines and pyrazolopyrimidines) and different claims from those at issue in the present application.

In the Office Action dated December 17, 2009, the Office failed to address Applicants' concerns that the reasons provided in support of the enablement rejection appeared to have been prepared based on a completely different application from Applicants' application. Instead the

Office dismissed the reference to "triazalopyrimidines and pyrazolopyrimidines" as a mere "typographical error."

Further information has come to Applicants' attention, however, that reinforces Applicants' suspicion that the rejection of the claims for lack of enablement was prepared based on consideration of an application that was completely unrelated to the present application, one that, in fact, that belongs to a different Assignee and addressing completely different subject matter from the present application.

It has come to Applicants' attention that on March 6, 2009, just three days before the Office Action of March 9, 2009 in the present Office Action issued, the Office issued an Office Action in Application 12/001,043, which is assigned to Amgen, Inc., ("the Amgen application") and relates to "Heterobicyclic Metalloprotease Inhibitors." The Office Action dated March 6, 2009 in the Amgen application included an enablement rejection. Despite the great differences between the subject matter, claims and disclosures of the two applications, the reasons provided in support of the enablement rejection made in the Office Action mailed on March 9, 2009 in the present application was strikingly similar to the reasons provided in support of the enablement rejection in the Amgen application. Applicants note, in particular, that in the enablement rejection made in the March 9, 2009 Office Action in the present application is largely word-for-word identical with the enablement rejection made in the March 6, 2009 Office Action in the Amgen application. In particular, the paragraphs discussing the *Wands* factors beginning on p. 7 line 9 of the present application and p. 6 line 1 of the Amgen application are identical – both stating that the present application describes how to make "triazalopyrimidines and pyrazolopyrimidines" despite the absence of any explicit discussion of such compounds in the present application. The two rejections are so similar that it was apparent that the rejection of the claims of the present application was prepared by making only minor alterations to a form rejection prepared for rejecting the claims of the Amgen application.

Based on the foregoing, the record is unclear to what extent – if any – the Office has actually considered the disclosure of the present application in considering the question of enablement of the claims of the present application. While it is apparent that the Office has

referred to the present application to provide suitable text for substituting into the enablement rejection form that it prepared for the application (for example, substituting a generic formula from the present application for the generic formula of the Amgen application in the otherwise identical paragraph entitled "Scope of the claims"), it is not apparent that the Office has given *bona fide* consideration to the disclosure of the present application when considering the question of enablement.

c. Compound Scope

It appears that the Office continues to allege that the examples provided in the specification are insufficient to support enablement of the full scope of the compound claims as defined in claim 1. The Office acknowledges that the compounds are adequately supported wherein the ring N-A-B-D is piperidinyl or piperazinyl and wherein Ar_1 is a phenyl or fused phenyl ring, but does not acknowledge support wherein the ring is other than piperidinyl or piperizinyl or Ar_1 is other than phenyl or fused phenyl. Office Action dated December 17, 2009 p. 3. The only reasons provided in support of the conclusions regarding compound scope are (1) the allegation that Applicants have not provided working examples other than those for which enablement has been acknowledged (Office Action dated March 9, 2009 p. 9) and that such exemplification is required for enablement; and (2) the allegation that "chemistry is unpredictable." (Office Action dated March 9, 2009 p. 8).

The primary factor underlying the Office's conclusion that the specification did not adequately enable the full scope of the claims appears to be that Applicants have allegedly not provided working examples of each and every one of the options provided for by the Markush formula of claim 1. For Example, the Office Action dated March 9, 2009 stated:

> *3) Number of working examples.* The compound core depicted with specific substituents represents a narrow subgenus for which applicant has provided sufficient guidance to make and use; however, this disclosure is not sufficient to allow extrapolation of the limited examples to enable the scope of the compounds instantly claimed or preventive agents. Applicant has provided no working examples of any compounds, compositions or pharmaceutically acceptable salts where the R variables were not those mentioned above in the present application.

> Within the specification, "specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. Markush claims must be provided with support in the disclosure for each member of the Markush group. Where the constitution and formula of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula." See MPEP 608.01 (p).

Office Action dated March 9, 2009, p. 9.

There is no basis in the law for the Examiner's apparently maintained position that every member of a Markush group needs to be included in a working example to provide adequate enablement. In *Ex Parte Hinze*, Appeal No. 2008-5635, slip op. at 7-8 (Bd. Pat. App. & Int., Jan. 29, 2009) the Board of Patent Appeals and Interferences *reversed* an enablement rejection made on the grounds, *inter alia*, that not all substituent options were exemplified and stating that "the question is whether the Specification gave sufficient guidance to make and use compounds having the listed substituents, *not whether working examples using all the substituents were provided*" (emphasis added). Applicants have made this point previously, yet their argument has not yet been addressed by the Office.

Applicants also have also pointed out the present application actually provides a substantial amount of guidance on how to make compounds of the present claims.

First, the Specification provides a Scheme in Figure 6 of a synthetic route applicable to preparing any compounds of the invention.

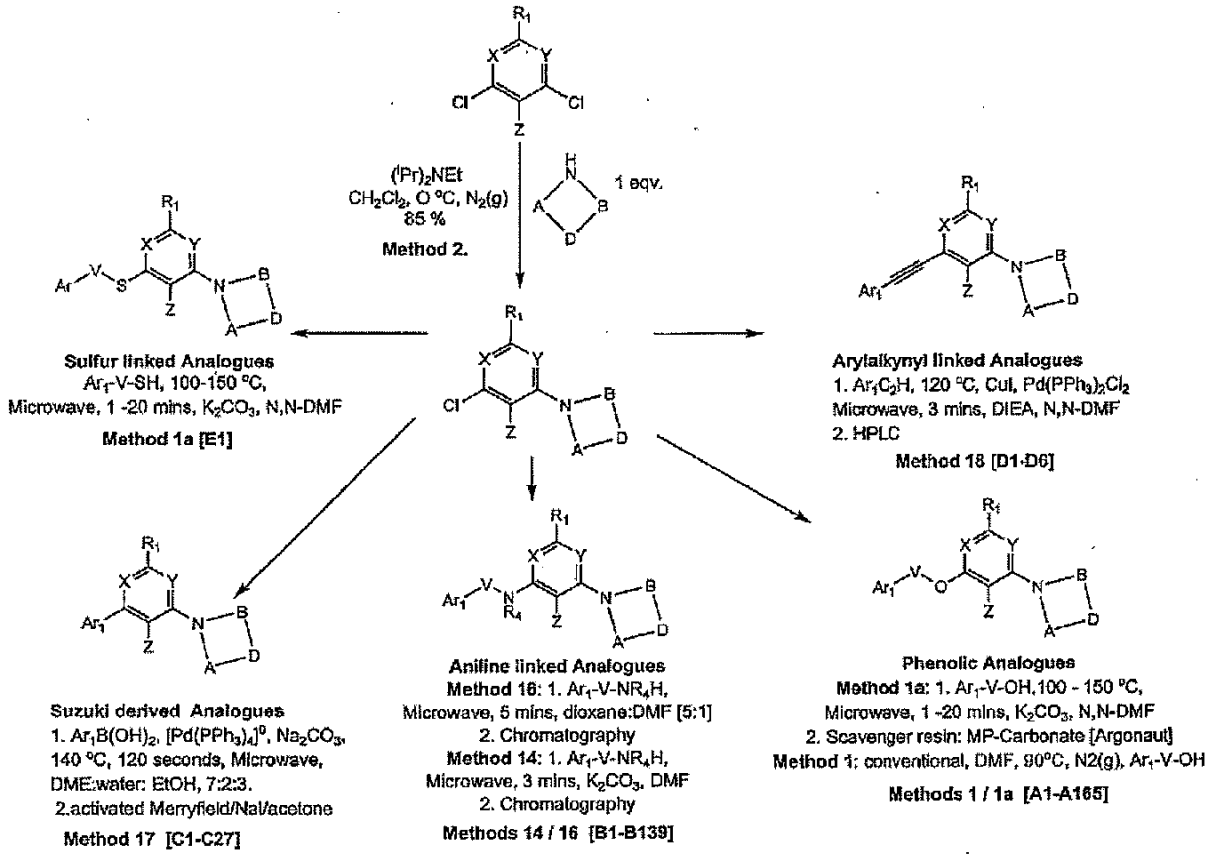
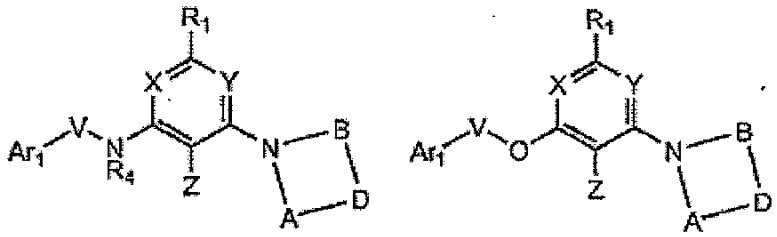
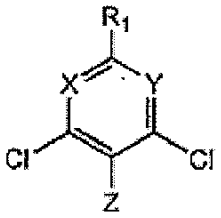


Figure 6

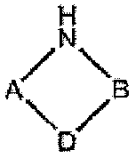
In view of the amendments limiting W to NR_4 or O, the relevant compounds are of the compounds of the following formulae:



The above scheme describes that the compounds can be prepared from an intermediate of the following formula:



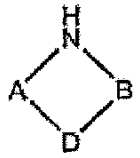
by performing nucleophilic substitution reactions of the chlorine atoms with a cyclic amine of the formula:



and aromatic amines and phenolic compounds. Since V is absent in the claims as amended, the required aromatic compounds are aromatic amines and phenolic compounds of the formulae:

Ar_1-NR_4H; and

Ar_1-OH.

Applicants respectfully submit that the nucleophilic aromatic substitution reactions required to perform the transformation are fully described in the examples, in addition to being well known in the art. The Office has not provided any reasons to suppose that the chemistry could not be successfully carried out with any compound of the formula 

required as a precursor of the N-A-B-D ring, or with any aromatic amine (Ar_1-NR_4H) or suitable hydroxyaromatic compound (Ar_1-OH) to provide any compound within the scope of the claims.

Applicants further point out that the specification on pages 127 to 222 describes in detail methods for making the compounds – including detailed instructions for synthesizing **over 300 Working Examples.** Furthermore, although Applicants are not required to provide working examples for every possible substituent option, the scope of the working examples provided still clearly goes beyond the scope that the Office has been willing to acknowledge to date as being enabled. For example, the compounds of the examples are not limited to compounds in which Ar_1 as phenyl or "fused phenyl" (see, e.g., Examples A2, A6, A7, A8, A9, A10, A11, A12, A13,

A14, A15, A19, A20, A21, A22, A25, A27, A31, A49, A66, A67, A68, A69, A78, A94, A95, A96, A97, A98, A99, A105, A106, A125, A126, A128, A148, A163, B83, B127, B129, B134, B135, B136, B137 and B139) or N-A-B-D as piperidine or piperazine (see, e.g., Example A97). Thus, the examples go beyond the scope that the Office acknowledges as being enabled with respect to each of R^1, N-A-B-D and Ar_1.

Although the Office provided in support of the rejection supposed "evidence" in the form of a lengthy quote from Dörwald (which was alleged to support the Office's assertion that "chemistry is unpredictable"), the Office failed to respond to Applicants' remarks pointing out that the citation was not relevant to showing that the chemistry required to form compounds of the invention would be unpredictable. Applicants noted that the Office did not provide any reasoning establishing that the success of the synthetic reactions required to form the compounds of Formula I would be unpredictable and that Applicants' success in making hundreds of examples of such compounds clearly indicates that the relevant chemistry is not, in fact, unpredictable. Applicants further noted that Dörwald only describes that unexpected difficulties are often encountered in the syntheses of "structurally complex natural products" and that this statement does not provide any basis for the Office to conclude that undue experimentation would be required to make Applicants' compounds because Applicants' compounds are not "structurally complex natural products." Applicants also noted that Dörwald itself acknowledges that "most organic chemistry textbooks and research articles" describe "that organic chemical reactions proceed smoothly", so according to Dörwald *most* textbooks and research articles would indicate that the practice of organic synthesis is generally quite predictable (though difficulties might arise in the synthesis of "structurally complex natural products"). The Office failed to make any showing that the synthesis of compounds of the invention would be particularly challenging or problematic.

Since the disclosure of the present application provides general synthetic routes applicable to the synthesis of compounds of the invention, and over 300 working examples, Applicants respectfully submit that the disclosure of the present application more than adequately supports enablement of the full scope of the compounds encompassed by Formula Ia

of claim 1. Importantly, the Office has provided no evidence or reasoning inconsistent with enablement of the full scope of the compounds of claim 1.

d. Hydrates and other Solvates

Applicants continue to disagree that the Office has provided any evidence or reasons to meet its burden of production to sustain its allegation that the Specification does not reasonably provide enablement for the synthesis of solvates including hydrates of the claimed compounds.

The Office Action mailed on December 17, 2009 addresses this issue with the following remarks:

> [A]pplicants have argued that solvates and hydrates have been reasonably enabled, examiner disagrees. Vippagunta, et. al. does explain that solvates and hydrates do exist, yes, and goes on to state that as many as 1/3 of all pharmaceuticals MAY form hydrates or solvates. However, the Applicants have not shown in any reasonable way that they have enabled compounds to form solvates or hydrates, they merely believe that some of them will form arguing probability. Applicants have not pinpointed which compounds will form a solvate, which will form a hydrate, which may form both and which will form neither. They merely speculate that because there is a chance of formation, that this must be good enough. Applicants must teach the current invention limitation of solvates and hydrates, which they do not. Vippagunta states that the formation of solvates and hydrates is unpredictable, therefore merely stating that exposing a compound to water or a solvent will generate the hydrate or solvate is completely false, as stated prior, 2/3 of all pharmaceuticals will NOT form the hydrate or solvate.

Office Action dated December 17, 2009.

Applicants respectfully point out that according to the law that pertains to the enablement requirement as established by the Federal Circuit Cout of Appeals, and as set forth in the MPEP (*see* MPEP 2164.04), patents Applicants are entitled to a presumption that the specification, which discloses how to make and use the claimed invention, complies with the first paragraph of 35 U.S.C. § 112. MPEP 2164.04 (citing *In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971)). This presumption applies unless and until the Office explains "why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which *is inconsistent* with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his

presumptively accurate disclosure." MPEP 2164.04 (citing *In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971)).

The Office's remarks, by apparently requiring Applicants to "show[ ] ... that they have enabled compounds to form solvates or hydrates" continue to evidence the Office's improper disregard of the presumption of enablement and improper attempts to shift the burden to Applicants to prove enablement of their claims when the Office has provided no evidence whatsoever to demonstrate that compounds of the invention would not be capable of forming solvates or hydrates. Since enablement is to be presumed as a matter of law, absent contrary evidence, and the Office has not presented any evidence whatsoever showing that solvates of compounds of the invention could not be formed, the Office has provided no basis for shifting the burden to Applicants to prove enablement of the claims.

The Office's remarks with respect to the question of enablement of solvates or hydrates continue to focus on only one of the *Wands* factors, namely the supposed unpredictability of solvate or hydrate formation, while disregarding all the other factors.

Nothing in Vippagunta is inconsistent with enablement of Applicants' claims. Applicants respectfully point out that. Vippagunta does not state that "2/3 of all pharmaceuticals will NOT form the hydrate or solvate" as the Office alleges. Vippagunta, in fact, states: "[i]t has been estimated that approximately one-third of pharmaceutically active substances are capable of forming crystalline hydrates." Far from emphasizing the difficulty of making solvates and hydrates, Vippagunta emphasizes their ubiquity. Applicants have provided hundreds of examples of pharmaceutically active compounds of the claimed invention, and thus, according to Vippagunta, is likely to describe many compounds capable of forming hydrates and solvates. Such compounds could be identified through no more than routine screening, as discussed below.

Vippagunta would therefore provide the person skilled in the art with no reason to believe that compounds according to the invention would be incapable of forming solvates or hydrates, and, to the contrary, suggests that many compounds of the invention would be capable of forming solvates and hydrates. Although the Office alleges that "Applicants have not pinpointed

which compounds will form a solvate, which will form a hydrate" the Office has failed to provide any evidence that "pinpoint[ing] which compounds will form a solvate [and] which will form a hydrate" would require anything more than routine experimentation. The Court of Appeals for the Federal Circuit has explicitly held that a need for routine experimentation such as routine screening is in no way inconsistent with the enablement requirement. *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988) ("Enablement is not precluded by the necessity for some experimentation such as routine screening.")

Even if the specification of the present application does not explicitly describe working examples in the form of solvates, it is important to realize that this does provide any indication or evidence that the compounds would not be capable of forming solvates. The methods usually used for purification of compounds in drug discovery, as described in the examples (typically by chromatography followed by evaporation of the product-containing fractions under reduced pressure) do not involve crystallization under the conditions which would form solvates. Furthermore, routine characterization of compounds in the drug discovery process – typically by ^{1}H NMR and mass spectrometry, typically focuses on confirming that the compound has been formed, and the medicinal chemist does not typically attempt to identify whether the compound is present in the form of a solvate. Thus, the fact that the specification does not explicitly state whether compounds of the invention were isolated in the form of solvates in no way indicates that compounds of the invention would not be capable of forming solvates.

Compounds containing the pyrimidine core of the claimed compounds existing in the form of hydrates are, however, well known in the art. For example, the following pyrimidine compounds, which are commercially available from the Sigma Aldrich Chemical Company exist in the form of hydrates:

4,6-diamino-2-mercaptopyrimidine hydrate (catalog no. 125830)

2-amino-6-chloro-4-pyrimidinol hydrate (catalog no. 07460)

2-amino-6-hydroxy-2-mercaptopyrimidine monohydrate (catalog no. A57406)

4,5-diamino-6-hydroxy-2-mercaptopyrimidine hemisulfate salt hydrate (392464)

while Quesada, et al, *Acta Cryst*, 2003, C59, o102-o104 describe the following compound as existing in the form of a monohydrate:

2-amino-5-nitro-4,6-dipiperidinopyrimidinium hydrogensulfate monohydrate.

Copies of Sigma-Aldrich Catalog pages showing the above compounds and an abstract of the Quesada reference are attached. Thus there is no reason to suppose that the pyrimidine compounds of the invention would be incapable of forming hydrates or solvates.

Nothing in Vippagunta is inconsistent with the existence of solvates and hydrates of the presently claimed compounds. The Office highlighted the following remarks in Vippagunta:

> "Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds. Certain molecular shapes and features favor the formation of crystals without solvent; these compounds tend to be stabilized by efficient packing of molecules in the crystal lattice, whereas other crystal forms are more stable in the presence of water and/or solvents. There may be too many possibilities so that no computer programs are currently available for predicting the crystal structures of hydrates and solvates." Vippagunta et. al. Advanced Drug Delivery Reviews 48 (2001) 3-26.

Vippagunta's remarks focus largely on the difficulty of predicting the structure and stability of solvates (e.g. "the number of molecules of water or solvent"). The claims, however, do not recite having a particular number of solvent atoms, or a particular structural lattice. Applicants' claims, in fact, do not recite any particular features of hydrates and solvates that they encompass, or even that such hydrates or solvates need to be stable. Rather, the claims merely recite solvates and hydrates to emphasize that the claims are intended include all forms of the compounds defined in claim 1, including any hydrate or solvate forms. Even if solvate formation were somewhat unpredictable, as the Examiner contends, the claims would still satisfy the enablement requirement because such experimentation as might be required to prepare salts or hydrates of the compounds of the invention would be routine and well within the capacity of the skilled artisan, and would therefore not be undue. As Applicants have pointed out, forming solvates and hydrates is far easier and more predictable than complex, unpredictable antibody technology described in *Wands* where the Federal Circuit reversed a finding of non-enablement,

holding the claims to be enabled as a matter of law. The court in *Wands* made the point that all the methods needed to practice the invention were well known, and the amount of effort was not excessive enough to be undue *despite any unpredictability* associated with making antibodies. *In re Wands*, 858 F.2d 731, 740 (Fed. Cir. 1988).

Applicants have provided evidence indicating that making solvates and hydrates is easy, simple, requires few steps, and demands little time, and that the person of skill in the art routinely engages in such experimentation, and that the techniques for performing such experimentation are well known.

To make hydrates and solvates, samples of the organic compound are simply exposed to water or various different solvents. Exposure of the organic compounds to water and various solvents is conducted through simple and routine methods such as letting the samples sit open to air for set amounts of time, as well as slurrying and/or crystallizing the samples from water or solvent. Other typical procedures for making and identifying hydrates and solvates are described on pages 202-209 of K.J. Guillory, "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids," in: Polymorphism in Pharmaceutical Solids, ed. Harry G. Brittan, Vol. 95, Marcel Dekker, Inc., New York, 1999 (of record).

Once solvates and hydrates are formed, they can be readily analyzed by routine methods. Examples of such techniques include thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), Karl Fischer titrimetry, X-ray diffractions (single crystal or powder), infrared spectroscopy (IR), polarized light microscopy, and hot stage microscopy or other routine techniques to detect and quantify the presence of solvate molecules in the sample. As evidence thereof, see page 18, right column, Vippagunta (of record).

Applicants have also provided evidence that solvate and hydrate form is so routine as to be amenable to high throughput crystallization as described, for example, in Morisette, *et al.*, *Adv. Drug Delivery Rev.*, **2004**, *56*, 275-300 (of record).

The Office Action attempts to base its enablement rejection solely on the alleged unpredictability of solvate formation and the fact that no specific examples of solvates have been described in the specification. *Wands* establishes that unpredictability (which was the main

grounds of improper enablement rejection in *Wands*), even if it were established, is not dispositive. Also, there is no requirement for a "working" example if the disclosure is such that one skilled in the art can practice the claimed invention. *In re Borkowski*, 164 U.S.P.Q. 642 (C.C.P.A. 1970); *Ex parte Nardi*, 229 U.S.P.Q. 79 (Pat. Off. Bd. App. 1986). Given that one skilled in the art could make and identify various hydrates and solvates of a particular organic molecule using the routine screening methods discussed above, no working example is necessary to enable the invention. *Wands*, in fact, mandated that numerous factors be considered in evaluating enablement rather than the narrow approach taken by the Office here.

It is respectfully submitted that any unpredictability or the absence of examples of solvates specifically described as solvates or hydrates should be found to be clearly outweighed by the other factors considered in *Wands*.

e. Properly Considering the *Wands* Factors Together Should Lead to a Conclusion That The Claims are Adequately Enabled.

In rejecting the claims, the Office has unduly emphasized certain *Wands* factors while disregarding others, and failed to indicate how certain factors were considered to outweigh others in reaching the conclusion that the claims lacked adequate enablement. For example, the Office emphasized the supposed unpredictability in the art as a factor supporting lack of enablement. However, the Office also indicated that the level of skill in the art is high, a factor that clearly supports enablement. The Office has continued in its failure to consider the state of the prior art supportive of enablement (e.g. the known, routine methods for preparing and screening solvates, for example). The Office does not explain why the factor of unpredictability, even if present, should outweigh all the other factors in reaching the conclusion of non-enablement. The Office continues to focus on a single factor (the supposed unpredictability of forming solvates and hydrates) to the exclusion of all others. The Office's approach to the enablement analysis is completely at odds with the proper approach to the question of enablement mandated by *Wands*.

Applicants submit that a careful consideration of the relevant factors under *Wands* should lead to a conclusion that Applicants' specification provides a more than adequate description of

how to make the invention, and that the Office heretofore has erred in its evaluation of these factors:

i. Breadth of the Claims.

The Office characterizes the claims as broad because they allegedly encompass "millions of compounds". However, the number of possible embodiments is not necessarily indicative of an unduly broad claim: even the narrowest and simplest of claims may be susceptible of many possible variations such that it compasses thousands, millions, or even an infinite number of possible embodiments. The Office's characterization disregards the *close structural relationship between the compounds encompassed by the claims*, and the common chemical synthesis routes applicable to synthesis of the compounds resulting from the analogous chemical functionalities of the compounds within the scope of the formula which would permit analogous routes to be used in preparing such compounds. As amended, the claims are directed to a narrow class of 4,5,6-trisubstituted pyrimidines. Many diverse compounds according to the invention could be synthesized from the same common intermediates, as is shown, for example by the synthetic scheme shown in Figure 6.

The person skilled in the art of medicinal chemistry will be familiar with the concept of combinatorial chemistry, or "multiple parallel synthesis" in which multiple analogous compounds can be synthesized in parallel by routine chemical manipulations to make "chemical libraries" of compounds, which can contain hundreds or thousands of compounds at a time, particularly when the compounds are closely structurally related and capable of being prepared via common intermediates as in the present application. Thus, the fact that a number of compounds might be encompassed by a claim would not necessarily indicate that the compounds would require an excessive amount of experimentation to prepare (assuming there would be a reason synthesis of more examples was required).

Due to the close structural relationship of the compounds claimed, the narrow breadth of the claims is a factor which clearly supports enablement.

ii. The Level of Skill in the Art.

The Office states that the "artisan using Applicants invention would be a chemist with a Ph.D. degree, and having several years of bench experience."

It appears, therefore that the Office is asserting that the level of skill in the art is high. Thus, this factor also supports a conclusion of enablement.

iii. Nature of the invention.

The Office characterizes the claims as being directed to "certain 1,2,3-trisubstituted aryl and heteroaryl derivatives that are modulators of glucose metabolism... useful in the prophylaxis or treatment of metabolic disorders and complications thereof, such as, diabetes and obesity." The claims under consideration are directed to organic chemical compounds for medicinal use.

Given that the Office has already acknowledged the high level of sophistication of the person skilled in the art of organic and medicinal chemistry, the nature of the invention is a factor that clearly supports enablement.

iv. The Level of Predictability in the Art.

The Office emphasizes the supposed unpredictability of the art, which appears to be the main reason emphasized by the Office in making the rejection.

With respect to the synthesis of compounds, as described in detail above Applicants respectfully disagree that there is any evidence that the reactions and synthetic schemes required to prepare compounds according to the invention is unpredictable. Applicants have shown the synthesis of about 300 examples of compounds which are within the scope of the claims (or similar to such compounds) in the application.

As noted above, the quotation from Dörwald cited as evidence that "chemistry is unpredictable" does not relate to the chemical reactions required to synthesize compounds of the invention, and the reference does not state that chemistry generally is unpredictable. Dörwald describes that the "most organic chemistry textbooks and research articles" teach "that organic chemical reactions proceed smoothly", indicating that *most* textbooks and research articles indicate that the practice of organic synthesis is quite predictable. Dörwald's observations

concerning the unpredictability that may be encountered in the syntheses of "structurally complex natural products" does not provide any basis for concluding that undue experimentation would be required to make Applicants' compounds because Applicants' compounds are not "structurally complex natural products".

As was also noted, Vippagunta emphasizes the ubiquity of solvates – stating that one third of pharmaceutically active substances are capable of forming crystalline hydrates:

> *3.1. Introduction to solvates and hydrates*
>
> It has been estimated that approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates [68]. The water

Vippagunta p. 15, col. 1.

Vippagunta's focus on the difficulty of predicting *the structure and stability* of solvates does not weigh heavily against the enablement of the present claims since the claims do not recite solvates of particular structure or stability. Vippagunta predicts, however, that one-third of pharmaceutically active compounds will form solvates. Applicants do not understand the Office's emphasis upon, and the supposed relevance of the issue of whether the stability or exact structure of the solvates or hydrates can be predicted.

As was also noted above, predictability is only one of the factors to be considered in assessing enablement, unpredictability is not dispositive of the question of enablement. In the *Wands* case itself, making monoclonal antibodies was found to be *highly unpredictable* – much less predictable than forming solvates – but the court found the enablement requirement to be met *as a matter of law*, because of the routine methods of screening involved. As discussed below, as in *Wands*, routine methods of screening are available to identify solvates.

Therefore, unpredictability of the art is not a factor that weight in favor of lack of enablement.

v. The State of the Art.

The Office has cited Cocco and Griffith as describing 4,5,6-substituted pyrimidines similar to compounds according to the rejected claims. Therefore, according to the Office, compounds structurally similar to those being claimed are known. The Office does not indicate that such compounds are particularly difficult to synthesize.

Applicants have also presented evidence that straightforward methods are available for the synthesis and screening of solvate and hydrate forms of pharmaceutical compounds. The methods are so routine that they can be implemented in high throughput form to discover solvates and hydrates of large numbers of compounds.

Applicants have also provided evidence that compounds containing the pyrimidine core common to the present compounds are known exist in the form of solvates: several pyrimidine compounds sold by Sigma Aldrich are sold in the form of hydrates.

Therefore, the state of the art is clearly a factor which supports a finding of enablement.

vi. Amount of guidance provided by the Applicants.

The present application provides a tremendous amount of guidance to the person skilled in the art for practicing the invention claimed herein. The specification provides over 200 pages of such guidance. For example, on pages 4 to 90, an exceedingly detailed account of compounds of the invention, including the embodiments and examples thereof, is provided. On pages 90 to 113, a detailed account of the utility of the compounds of the invention is provided, including guidance on how to formulate the compounds and suitable dosages. Then, on pages 113 to 126, numerous assays for evaluating the compounds are provided. On pages 127 to 222, methods of synthesizing **over 300 Examples** of compounds representative of the invention are provided. Figure 6 provides a comprehensive synthetic scheme describing how to make compounds of the Application. It is not seen that the Office has any basis to doubt the adequacy of the disclosure.

The extensive guidance provided by the Applicants is clearly a factor which weighs in favor of a finding of enablement.

vii. Number of working examples.

As the Applicants pointed out above, the present specification describes over **300 working examples** of structurally diverse compounds within the scope of the invention, or structurally similar compounds, despite the fact that there is no requirement that Applicants provide any working examples to satisfy the enablement requirement.

The large number of working examples provided by the Applicants is again a factor weighing in favor of enablement.

viii. The Amount of Experimentation Needed to Make the Invention.

Applicants respectfully submit that, in view of the foregoing factors, the amount of experimentation required to carry out the claimed invention with the guidance provided by the 250 page specification and 300 working examples would be by no means undue. The specification describes methods of making compounds of the invention and screening them for relevant biological activity. Solvates of pharmaceutically active compounds are ubiquitous and methods of preparing and screening for solvates are straightforward and routine in the extreme.

In view of the foregoing factors and the high level of skill in the art, it would require no more than routine experimentation – synthesizing compounds and routine screening – to practice the invention of the rejected claims.

In view of all the foregoing remarks, the Applicants respectfully request that the rejection of claims under the enablement requirement of 35 U.S.C. § 112, first paragraph.

2. Rejection of Claims 1-3, 12-14, 16-61, 73, 74 and 78 under 35 U.S.C. § 112, Second Paragraph

Claims 1-3, 12-14, 16-61, 73, 74 and 78 were rejected under 35 U.S.C. § 112, second paragraph as being allegedly indefinite. The Applicants respectfully request reconsideration of the rejection. The basis provided for the rejection is that certain terms that are said used in the claims are allegedly not clear. The allegedly unclear terms are "heteroaryl" and "heterocyclic."

The Office Action provides the following reasons to justify the rejection:

> The terms are defined vaguely with non-limiting examples making them impossible to determine. For example, when one states, "heterocyclic" and then

> provides a list of well over 30 examples and states the list is "non-limiting", how can this be considered definite? One skilled in the art could instantly envision well over one hundred ring systems that qualify under this vague definition. Does the applicant wish to claim a thiophene, triazolopyrimidine or a [1,2]oxazino[6,5,4-de][2,6]naphthyridine? If the ring desired is a pyridine ring, is it 2-pyridyl, 3-pyridyl, or 4-pyridyl ring? Applicant must narrow such broad terminology by either eliminating such a vague definition or by inserting the specific ring systems they wish to cover into the claim themselves.

Office Action dated December 17, 2009, at pp. 4-5.

Applicants respectfully point out that the Office's characterization of the terms "heteroaryl" and "heterocyclic" as being "vague and is defined only by non-limiting examples within the specification" is simply incorrect. The Specification, in fact, provides an *explicit definition* of the term "heteroaryl" and "heteroaryl" so these terms are therefore not "defined only by non-limiting examples." In particular, the specification provides the following definition on p. 16 of the specification as filed *in addition to* providing examples of "heteroaryl" groups:

> The term "**heteroaryl**" denotes an aromatic ring system that may be a single ring, two fused rings or three fused rings containing carbons and at least one ring heteroatom selected from O, S and N.

Similarly, the Specification provides the following definition, also on p. 16 of the specification as filed, of the term "heterocyclic":

> The term "**heterocyclic**" denotes a non-aromatic carbon ring (i.e., cycloalkyl or cycloalkenyl as defined herein) wherein one, two or three ring carbons are replaced a heteroatom, such as, O, S, N, wherein the N can be optionally substituted with H, C_{1-4} acyl or C_{1-4} alkyl, and ring carbon atoms optionally substituted with oxo or a thiooxo thus forming a carbonyl or thiocarbonyl group. The heterocyclic group is a 3-, 4-, 5-, 6- or 7-membered containing ring.

Thus, in the present application, an *explicit definition* of each of the terms "heteroaryl" and "heterocyclic" is provided. Neither of these terms is "vague and ... defined only by non-limiting examples" within the specification of the present application. Applicants fail to see, and the Office has failed to explain, why the Office might consider these definitions to be unclear, and the definitions are explicit definitions, not definitions that refer to "non-limiting examples."

The Office is respectfully reminded of the legal standards governing a rejection under 35 U.S.C. § 112, second paragraph. MPEP 2173.02 explains that the focus of the inquiry for

compliance with the requirement for definiteness "is whether the claim meets the threshold requirements of clarity and precision, not whether more suitable language or modes of expression are available." The Office "should allow claims which define the patentable subject matter with a *reasonable* degree of particularity and distinctness." The Court of Appeals for the Federal Circuit has explained that "The requirement to 'distinctly' claim means that the claim must have a meaning discernible to one of ordinary skill in the art when construed according to correct principles. Only when a claim remains insolubly ambiguous without a discernible meaning after all reasonable attempts at construction must a court declare it indefinite." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1366 (Fed. Cir. 2004). When a claim "is not insolubly ambiguous, it is not invalid for indefiniteness." *Bancorp Services, L.L.C. v. Hartford Life Ins. Co.*, 359 F.3d 1367, 1372 (Fed. Cir. 2004) (citing *Honeywell Int'l, Inc. v. Int'l Trade Comm'n*, 341 F.3d 1332, 1338-39 (Fed. Cir. 2003). "[C]laims need not 'be plain on their face in order to avoid condemnation for indefiniteness; rather, what [is] asked is that the claims be amenable to construction." *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1340 (Fed. Cir. 2005)(citing *Exxon Research & Eng'g Corp. v. United States*, 265 F.3d 1371, 1375 (Fed. Cir. 2001)).

Applicants respectfully submit that, in view of the explicit definitions provided in the specification, neither of the terms "heteroaryl" or "heterocyclic" can legitimately be said to be "insolubly ambiguous" or not "amenable to construction." Rather, the meaning of each of these terms is clear in light of the explicit definitions set forth in the claims.

The only reasons provided in the Office Action in support of the rejection focus on the supposed breadth of these terms as the only rationale supporting the indefiniteness rejection, disregarding the MPEP's explicit instruction that "[b]readth of a claim is not to be equated with indefiniteness. MPEP 2173.04 (citing *In re Miller*, 441 F.2d 689, 169 U.S.P.Q. 597 (C.C.P.A. 1971)). Despite this unambiguous instruction in the MPEP, the Office Action clearly and improperly equates indefiniteness with breadth – as is apparent from the Office Action's statements such as "Applicant must *narrow* such broad terminology either by eliminating such a vague definition or inserting the specific ring systems they wish to cover in the claim (sic)

themselves." Office Action dated December 17, 2009 at pp. 4-5 (emphasis added). Applicants fail to see how eliminating the explicit and clear definitions of "heteroaryl" or "heterocyclic" provided in the specification could possibly improve the clarity of the claims. Rather, the meaning of the claims in general and these terms in particular are already perfectly clear in light of the explicit definitions already provided on p. 16 of the specification.

Applicants note that the reasons provided in support of the indefiniteness allegation fail to point to any ambiguity in the meaning of the terms "heteroaryl" and/or "heterocyclic" or the definitions of these terms. The Office Action on p. 4 poses some (one assumes rhetorical) questions regarding the meaning of the terms – yet fails to point to any ambiguity in the meaning of the claims the Office might intend these questions to reveal. In fact, the answer to these questions is apparent from the definitions provided in the Specification. For example, the Office is correct to point out that a pyridine can be attached via the 2-, 3- or 4-positions. In each of these possibilities, the pyridyl remains within the definition of a "heteroaryl" group as set forth in the specification. A pyridyl ring is aromatic and contains a heteroatom (nitrogen) when it is attached via the 2-, 3- or 4-positions. Nothing is made unclear about the term "heteroaryl" from the fact that such a group may have more than one possible point of attachment. Nothing about this fact makes the scope of the term "heteroaryl" insolubly ambiguous to the person skilled in the art.

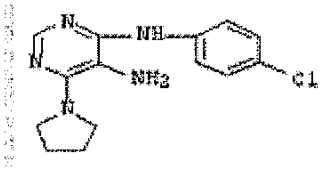
In summary, therefore, although the Office has maintained the rejection of claims 1-3, 12-14, 16-61, 73, 74 and 78 under 35 U.S.C. § 112, second paragraph, Applicants continue to traverse the rejection. Applicants note that the rejection appears to be founded on both factual and legal errors. The factual error is that the assertion that the terms "heteroaryl" and "heterocyclic" are "defined only by non-limiting examples within the specification." This is not the case, as the specification provides an explicit definition of the terms "heteroaryl" and "heterocyclic" as well as examples of "heteroaryl" groups and "heterocyclic" groups on p. 16. The legal error is that the Office has failed to establish any respect in which these terms are ambiguous, and bases the rejection on reasoning that improperly equates breadth and

indefiniteness (e.g. as reflected in the suggestion that "Applicant must *narrow* such broad terminology.")

Applicants therefore respectfully ask that the rejection once again be reconsidered, taking account of the explicit definitions provided on p. 16 of the specification. If, however, the Office continues to consider that these terms are not clear, Applicants would continue to welcome any suggestions that the Office might have as to how the clarity or precision of the claims could be improved.

3. Rejections of Claims 1-3, 12, 16 and 78 under 35 U.S.C. § 102(e) Over Griffith

Claims 1-3, 12, 16 and 78 were rejected under 35 U.S.C. § 102(e) as being allegedly anticipated by Griffith, et al., WO 2004037823 ("Griffith"). The Office Action alleges that the reference discloses the following compound on p. 84 of the specification:



"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP 2131 (citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987).

As a preliminary matter, Applicants do not concede that the reference cited is prior art against the present application. Applicants note that the referenced application was filed on October 21, 2003. The present application has an international filing date of January 14, 2004, but claims priority to provisional applications filed prior to the filing of the Griffith reference, namely 60/470,875 (filed May 14, 2003), 60/453,390 (filed March 6, 2003), 60/449,829 (filed February 24, 2003) and 60/440,394 (filed January 14, 2003). The Office has made no showing that the cited disclosure of Griffith is prior art against the present claims.

Moreover, the cited disclosure of Griffith, even if prior art, would not anticipate the claims because the description of the compound cited in the Office Action does not include each and every element of the compounds claimed in the rejected claims. The Office alleges that the

above-cited compound, said to be disclosed on p. 84 of Griffith, anticipates the claims as a compound within the scope of the claims wherein X and Y are N, W is NH, V is absent, Ar_1 is a 4-chlorophenyl ring, R_1 is hydrogen, Z is an amino group and the N-A-B-D ring is pyrrolidinyl ring. Applicants respectfully point out, however, that the disclosure of the above-cited compound would be insufficient to anticipate the claims of the present application under 35 U.S.C. § 102(e), at least because the compound cited in the Office Action *lacks a group corresponding to D in the N-A-B-D ring*. Applicants point out the definition of D in claim 1 is CR_2R_3 or N-R_2 and that no such group meets the definition of D in the compound cited in the Office Action, whose structure is given above, because R_2 may not be hydrogen.

Since the compound cited in the Office Action does not meet each and every element of the claims, and since the Office has not identified any other compounds in Griffith that do meet each and every element of the claims, Applicants respectfully submit that the rejection made under 35 U.S.C. § 102(e) is improper. Applicants therefore request that the rejection be withdrawn.

IV. Conclusion

Applicants respectfully request reconsideration of the grounds of rejection in light of the above comments. Further, early reconsideration and allowance of all pending claims is respectfully requested. It is believed that any pending objections and rejections have been addressed. If, at any time, it appears that a phone discussion would be helpful to resolve any outstanding issues, the undersigned would appreciate the opportunity to discuss any such issues at the Examiner's convenience.

The Commissioner is hereby authorized to debit any fee due or credit any overpayment to Deposit Account No. 06-1050 quoting Attorney's Docket No. 20750-0007US1 / 034.US5.PCT. Even if not accompanied by an independent petition, this paper constitutes a Petition for an Extension of Time for an amount of time sufficient to extend the deadline and authorizes the Commissioner to debit the petition fee and any other charges or credits to Deposit Account No. 06-1050 referencing docket number Attorney's Docket No. 20750-0007US1 / 034.US5.PCT.

Respectfully submitted,

Date: March 17, 2010

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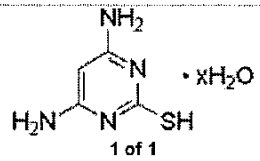
Image



1 of 1

125830 4,6-Diamino-2-mercaptopyrimidine hydrate

Aldrich 99%

★★★★★
Be the first to write a review.

Price and Availability

Product Number	Your Price USD	Available to Ship	Quantity	Actions
125830-25G	54.40	03/16/2010	details...	
125830-100G	142.00	03/16/2010	details...	

Synonym: 4,6-Diamino-2-pyrimidinethiol
CAS Number: 1004-39-3 (anhydrous)
Linear Formula: $C_4H_6N_4S \cdot xH_2O$
Molecular Weight: 142.18 (anhydrous basis)
MDL number: MFCD00149406
PubChem Substance ID: 24847680

Details Related Products References Reviews

Description

Packaging 25, 100 g in poly btl

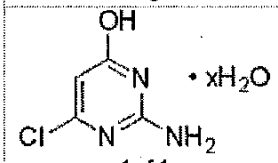
Properties

assay 99%
mp >300 °C(lit.)

Safety

Personal Protective Equipment Eyeshields, Gloves, type N95 (US), type P1 (EN143) respirator filter
WGK Germany 3

Image



1 of 1

07460 2-Amino-6-chloro-4-pyrimidinol hydrate

Fluka purum, ≥98.0% (AT)

☆☆☆☆☆
Be the first to write a review.

Price and Availability

Product Number	Your Price USD	Available to Ship	Quantity	Actions
07460-25G	236.00	03/17/2010 details ..		

Synonym:	2-Amino-4-chloro-6-hydroxypyrimidine hydrate
CAS Number:	206658-81-3
Linear Formula:	$C_4H_4ClN_3O \cdot xH_2O$
Molecular Weight:	145.55 (anhydrous basis)
Beilstein Registry Number:	509212
EC Number:	214-785-4
MDL number:	MFCD00149407

Details Related Products References Reviews

Properties

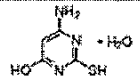
grade	purum
assay	≥98.0% (AT)
total impurities	5-15% water
mp	252 °C (dec.)(lit.)

Safety

Personal Protective Equipment dust mask type N95 (US), Eyeshields, Gloves

Hazard Codes	Xi
Risk Statements	36/37/38
Safety Statements	26-36
WGK Germany	3

Image



1 of 1

A57406 4-Amino-6-hydroxy-2-mercaptopyrimidine monohydrate

Aldrich 98%

★★★★★
Be the first to write a review.

Price and Availability

Product Number	Your Price USD	Available to Ship	Quantity	Actions
A57406-25G	21.70	03/16/2010 details ..		

Synonym:	6-Amino-2-mercapto-4-pyrimidinol monohydrate, 6-Amino-2-thiouracil monohydrate
CAS Number:	65802-56-4
Linear Formula:	$C_4H_5N_3OS \cdot H_2O$
Molecular Weight:	161.18
MDL number:	MFCD00150556
PubChem Substance ID:	24891014

Details Related Products References Reviews

Description

Packaging 25, 100 g in poly btl

Properties

assay 98%

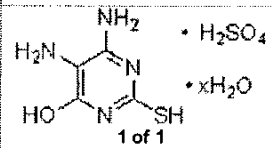
mp >300 °C(lit.)

Safety

Personal Protective Equipment dust mask type N95 (US), Eyeshields, Gloves

Hazard Codes	Xn
Risk Statements	22-36
Safety Statements	26
WGK Germany	3
RTECS	UW0495000

Image



1 of 1

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392464

Aldrich

4,5-Diamino-6-hydroxy-2-mercaptopyrimidine hemisulfate salt hydrate

97%

☆☆☆☆☆
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Price and Availability

Product Number	Your Price USD	Available to Ship	Quantity	Actions
392464-5G	29.60	03/16/2010 details ..		
392464-25G	111.50	03/16/2010 details..		

CAS Number: 304851-89-6
Linear Formula: $C_4H_6N_4OS \cdot 0.5H_2SO_4 \cdot xH_2O$
Molecular Weight: 207.22 (anhydrous basis)
MDL number: MFCD00191981
PubChem Substance ID: 24864456

Details | Related Products | References | Reviews

Description

Packaging 5, 25 g in glass btl

Properties

assay 97%
mp 235 °C (dec.)(lit.)

Safety

WGK Germany 3

Acta Crystallographica Section C

Crystal Structure Communications

Volume 59, Part 3 (March 2003)

organic compounds

Acta Cryst. (2003). C**59**, o102-o104 [doi:10.1107/S0108270103001458]

2-Amino-5-nitro-4,6-dipiperidinopyrimidinium hydrogensulfate monohydrate: hydrogen-bonded sheets containing highly distorted cations

A. Quesada, A. Marchal, J. N. Low and C. Glidewell

Abstract: In the title compound, $C_{14}H_{23}N_6O_2^+\cdot HSO_4^-\cdot H_2O$, the pyrimidinium ring of the cation adopts a twist-boat conformation, induced by steric clashes between adjacent ring substituents; the anions and the water molecules are linked by three O-H. . .O hydrogen bonds [H. . .O = 1.70-1.78 Å, O. . .O = 2.548 (2)-2.761 (2) Å and O-H. . .O = 161-168°] into chains of edge-fused $R_4^4(12)$ rings, which are linked into sheets by the cations, *via* three N-H. . .O hydrogen bonds [H. . .O = 1.96-2.17 Å, N. . .O = 2.820 (2)-2.935 (2) Å and N-H. . .O = 145-173°].

Formula: $C_{14}H_{23}N_6O_2^+\cdot HSO_4^-\cdot H_2O$